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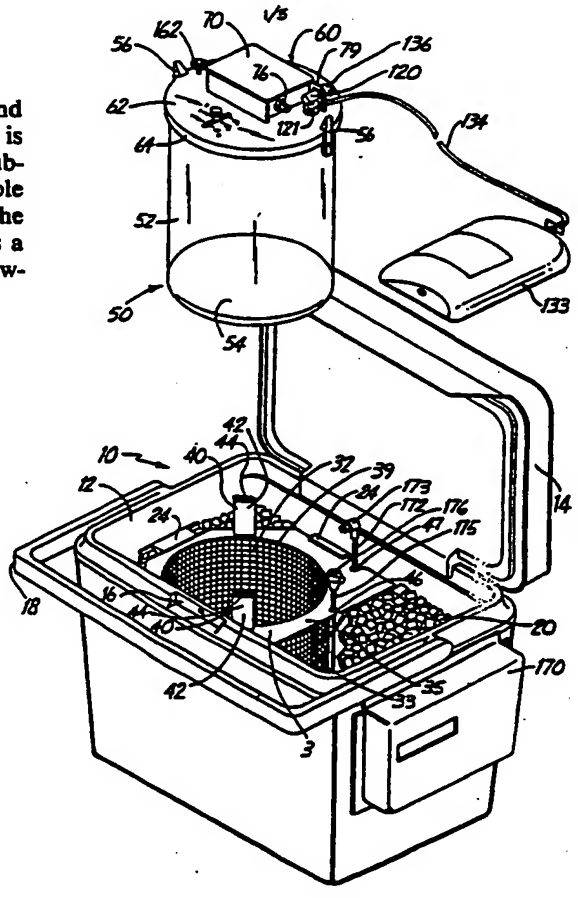
(54) Title: MICROPERFUSION APPARATUS

(57) Abstract

A transportable microperfusion device (10) for transporting and maintaining an excised heart for an extended period of time. The heart is suspended in a chamber (50) with the aorta in communication with a bubble trap (70). Perfusate flow from a perfusate reservoir (133) to the bubble trap (70) is maintained by a pumping and flow control system (170). The bubble trap (70) maintains an air-free aortic connection and maintains a column of perfusate sufficient to keep the aortic valve closed, thus allowing perfusate to be forced into the coronary arteries.



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MICROPERFUSION APPARATUS

FIELD OF THE INVENTION

This invention relates generally to the field of heart transplant surgery and particularly to devices for supplying perfusate solutions to hearts excised from donors to preserve the hearts until they can be transplanted into recipients.

BACKGROUND OF THE INVENTION

Successful heart transplantation depends in large measure upon the procedures that are taken to preserve viability of the heart during the quiescent period between the time that it is harvested from the donor until it begins to function after transplantation in a recipient. Whereas various other organs such as livers and kidneys can be preserved for many hours without significant loss of function, the heart muscle loses viability much more rapidly. In current practice, the maximum quiescent period for the heart muscle is about four to six hours.

It is not always possible to bring the proposed heart donor and recipient together in the same location; hearts that become available for transplantation often must be harvested quickly and transported swiftly to the recipient's location. On a practical basis, the heart must be preserved as well as possible in a container that can be transported by air. The container may simply contain a bath of an appropriate preservation solution at ice temperatures.

In clinical practice, the two situations in which cardiac preservation is required are heart transplantation and cardioplegia for open heart surgery. In heart transplantation, the donor heart is exposed through a midline sternotomy. After opening the pericardium, the superior and inferior vena cavae and the ascending aorta are isolated. The venous inflow is then occluded, the aorta is cross clamped, and approximately 1 liter of cold cardioplegic solution is flushed into the aortic root under pressure through a needle. As a result, the heart is immediately arrested, and cooling is supplemented by surrounding it with iced saline. The cold arrested heart is then surgically excised, immersed in cold cardioplegic solution, surround by ice and rushed to the recipient center.

The recipient's chest is opened through a midline sternotomy, and after placing the patient on cardiopulmonary bypass, the diseased heart is excised. The preserved donor heart is then removed from the preservation apparatus, trimmed appropriately and sewn to the stumps of the great vessels and the two atria in the chest. After completion of the vascular anastomoses, blood is allowed to return to the heart. It then will either resume beating spontaneously or will require chemical and electrical treatment to restore normal rhythm. When the heart is ready to take over the circulation, the cardiopulmonary bypass is discontinued and the recipient's chest closed.

It is generally understood that "living" organs, including the heart, continue the process of metabolism after removal from the donor so that cell constituents are continuously metabolized to waste products. The accumulation of these metabolic waste

products, depletion of cell nutrients and consequent derangement of cell composition lead to progressive loss of function and ultimately to cell death if the storage technique is inadequate. That is, the organ will lose its ability to function adequately after transplantation into the recipient. Several procedures have been successfully explored to enable organs to be preserved ex vivo for useful time periods. In one method the organ to be transplanted is rapidly cooled by flushing cold solutions through the organ's vascular system and maintaining the organ at temperatures near 0°C for the purpose of greatly slowing the metabolic rate. In the case of the mammalian heart, the flush solution composition is designed to cause the heart to rapidly stop beating as well as to preserve it.

Another method for organ storage utilizes continuous perfusion at temperatures in the range of 7-10°C with an oxygenated solution designed to support oxidative metabolism and to remove waste products. A suitable perfusate is delivered through the circulatory system of the isolated organ - usually from the arterial side and as the perfusate is conveyed through the vascular system waste products are carried away from the organ. Kidneys and livers can commonly be preserved in this manner for several days. However, only limited success has been achieved in preserving the heart, and therefore this method is not used in clinical heart transplantation. The heart must function well enough to sustain a good circulation in the recipient immediately after the transplant operation, whereas some impairment of function can be tolerated in transplanted livers and kidneys. Since hearts can only be preserved for 4-6 hours using cardioplegic solutions, heart

transplantation tends to be ruled out in certain situations in which the proposed donor and recipient are far distant from one another.

The viability of a preserved organ depends on a number of factors, among which may be listed (1) cell swelling which occurs at low temperatures as water is transferred across cell membranes in a stored organ, (2) the degree of intracellular acidosis which occurs during non-perfused ice storage as a consequence of continued cell metabolism, (3) derangement of internal cell composition which results from impaired metabolism, particularly with respect to cations such as calcium, potassium, magnesium and sodium, and (4) injury caused by oxygen-derived free radicals during oxygenated perfusion or after restoration of the circulation.

Perfusate solutions containing hydroxyethyl starch ("HES") have been reported by Belzer and Southard in Transplantation, 45:673-676, April, 1988, for use in preserving the kidney, liver and pancreas. See also Belzer et al., U.S. patent no. 4,798,824, issued January 17, 1989. The compositions may vary depending on whether they are to be used for continuous perfusion or a single flush ice storage of the organ.

BRIEF DESCRIPTION OF THE INVENTION

The present invention provides an easily transportable microperfusion apparatus having particular utility in preserving excised hearts for extended periods of time well in excess of six hours while the heart is en route to the recipient's location and while appropriate donor/recipient blood and tissue matches are being performed.

The apparatus comprises a first chamber for receiving a heart muscle, the chamber including an aortic connection attachable to and communicating with the aorta of the heart and permitting the heart to be suspended within the chamber from the aortic connection. The apparatus includes a reservoir of perfusate solution, and conduit means communicating the reservoir with the aortic connection. The conduit means includes a positive displacement pump for pumping perfusate from the reservoir to the heart through the aortic connection at a controlled rate of from about 175 to about 3000 ml per 24-hour period, it being desired to supply perfusate solution to the heart at the controlled rate of from about 3.5 to about 6 ml/gram of heart weight/24 hr period. Cooling means are provided to maintain the heart muscle and the perfusate solution entering it at a reduced temperature, preferably in the range of about 0° to about 10°C.

The conduit means of the apparatus desirably includes a bubble trap receiving perfusate from the pump and comprising a chamber elevated above the aortic connection to receive air bubbles emitted from a heart suspended from the aortic connection, the bubble chamber including means permitting trapped air to be expelled therefrom so that the conduit between the pump and the aortic connection is maintained substantially air-free. Perfusate from the bubble chamber immediately replaces the volume occupied by escaping air bubbles. The chamber housing the heart includes means communicating the chamber with the atmosphere so that the heart-receiving chamber is maintained at ambient atmospheric pressure. The bubble trap maintains a column of perfusate at least 1 cm in height above the valve of the aorta to maintain

the aortic valve closed, the perfusate thus being forced into the coronary arteries (accessed at the root of the aorta) rather than into the left ventrical.

BRIEF DESCRIPTION OF THE DRAWING

Figure 1 is an exploded, perspective view, partially broken away, of a device of the invention;

Figure 2 is an exploded, perspective view of a bubble trap and valve assembly employed with the device shown in Figure 1;

Figure 3 is a perspective, broken-away view of a valve shown also in Figure 2;

Figure 4 is a perspective, broken-away view similar to that of Figure 3 but showing the valve in a different position;

Figure 5 is a perspective, broken-away view similar to that of Figures 3 and 4 but showing the valve in another position; and

Figure 6 is a schematic view of a device of the invention.

DESCRIPTION OF THE PREFERRED EMBODIMENT

The readily transportable apparatus of the invention is shown in Figure 1 as including a transport case (10) which desirably has insulative properties so that objects placed therein may be maintained at a cool temperature for extended periods of time. The inner walls of the transport case define a receiving well (12).

In a preferred embodiment, the receiving well desirably is generally parallelepiped in shape and includes a generally rectangular floor, opposed pairs of parallel walls defining an upwardly open cavity, and a hinged cover (14). The floor, walls and cover of the receiving well are insulated. A retaining latch (16) is provided to retain the cover in its closed position. The transport case may also include a pivotable handle (18), as shown.

The apparatus depicted in Figure 1 includes an internal brace (30) for retaining and supporting a heart chamber (50) within the transport case. The brace includes a canister (32) configured to receive the generally cylindrical heart chamber (50) depicted in Figure 1. The canister includes an upright, generally cylindrical and desirably perforated wall (33) and a circular bottom which may rest on the floor of the receiving well. The canister is desirably formed from a plastic mesh to facilitate the cooling of the heart chamber by the cooling media (e.g., crushed ice).

A platform (35) is supported adjacent to the top of the canister (32), and a plurality of retaining tabs (24) may be disposed on the inner surface of the walls of the receiving well (12) for engaging and supporting the platform. The platform includes a substantially circular opening (39) through which the heart chamber (50) is received.

The brace may also be provided with latches (40) for holding the heart chamber in the canister. In a preferred embodiment, the canister is shorter than the heart chamber so that the chamber cover (60) is disposed above the platform (35) when the chamber is fully received within the canister. The brace in this embodiment includes upwardly extending arms (42) having pivotally mounted fingers (44), movable between a locking position adjacent the upper surface of the chamber cover, and an open position disposed away from the cover. When the fingers are pivoted to their locked positions, movement of the chamber with respect to the brace is limited by contact between the finger and the chamber cover.

The heart chamber (50) has a generally cylindrical side wall (52) desirably formed of a clear

material through which the contents of the chamber may be viewed. A generally circular floor (54) is disposed adjacent, and sealed to the lower end of, the side wall. Cover retaining means such as hooks (56), may be employed to sealingly secure the cover (60) to the chamber. The hooks (56) may be pivotally attached to the side wall near the upper rim so that they may be pivoted into and out of contact with the cover. The hooks are preferably formed of a resilient material, such as a plastic, so that they may be disengaged from the cover simply by urging them radially outwardly. The chamber cover (60) comprises a generally circular top (62) and cylindrical side walls (64) sized to fit about the upper rim of the cylindrical side wall of the chamber. A bubble trap (70) is positioned on the upper surface of the cover top (62).

Referring to Figure 2, the bubble trap may be generally box-shaped, having a top (72) and four side walls (74,78,82,84) which are sealingly attached to one another. Through the first side wall passes a pump line port (75) to which may be fitted a delivery line connector (76). Side wall (78) has an extension (79) that extends past the first side wall when the bubble trap is assembled (best seen in Figure 1). A pair of openings are formed through the extension and define first and second prime valve supply ports (80), (81), the purposes of which will appear below.

The bubble trap (70) as illustrated includes a bottom plate (86) sealingly attached to each of the four side walls of the trap at a position spaced above the top member (62) of the cover, providing a substantially air-tight chamber carried above the cover. The bottom plate includes a perfusate supply port (88) and an elongated slot (90). The top cover

(62) includes a supply orifice (92) disposed beneath and aligned with the perfusate supply port (88); both of these openings desirably are circular.

The chamber cover (60) also includes a valve control (100), of which a preferred embodiment is shown in Figure 2. The valve control in this embodiment includes a valve slide plate (102) carried by and beneath the top member (62) of the cover. A supply orifice (104) is provided in the valve slide plate in line with the supply orifice (92) of the top member of the cover and with the perfusate supply port (88).

As described in more detail below, perfusate flows from the bubble trap (70) to the heart (not shown in Figure 2) via a perfusate supply tube (94) which passes through the supply ports 92 and 104. Top and bottom cuff portions (96,98, respectively) are formed at the tube ends. Preferably, the outer diameter of the supply tube is smaller than the diameter of the orifices (92, 104) so that the tube may be deformed within these orifices when the tube is crimped shut to prevent perfusate flow (as shown in Figure 3).

Top (106) and bottom (110) valve seal means are carried by the top (96) and bottom (98) cuffs, respectively, of the heart supply tube. Each valve seal means includes an inner ring (107,111) and an outer ring (108,112). The inner ring is carried between the doubled back cuff portion and the exterior of the tube, and the outer ring is disposed about the exterior of the cuff and may be adhered sealingly to the cuff with an adhesive such as a room-temperature vulcanizing (RTV) silicone. The cuff is thus firmly held between the inner and outer rings. The outer ring (112) of the bottom valve seal means sealingly

engages upwardly against the lower surface of the valve slide plate (102) about the supply orifice (104). The top valve seal means (106) is disposed between the top member (62) of the chamber cover and the bottom plate (86) of the bubble trap. The outer ring (108) sealingly engages the lower surface of the bottom plate (86) of the bubble trap about the supply port (88). Thus, the supply tube defines a sealed pathway for perfusate flow from the interior of the bubble trap downwardly through the bottom plate of the trap, the top member of the cover, and the valve slide plate.

A mounting ring (114) is sealingly attached to the bottom surface of the valve slide plate (102) about the bottom valve seal means (110). The mounting ring includes a hollow, generally cylindrical nozzle (115) which extends downwardly. The cylindrical member retains and may be fitted within an aortic connector, typified in the drawing as heart mounting shaft (117). In use, a heart to be preserved is sealingly attached by its aorta to the mounting shaft by known means, as by sutures. Once the heart is attached, the mounting shaft may be placed on the cylindrical nozzle of the mounting ring.

A preferred embodiment uses a press fit seal between the cylindrical nozzle (115) and the mounting shaft (117), but any other means, such as a threaded connection, may be used. This connection should be strong enough to bear the weight of the heart which is suspended by the shaft (117) within the chamber (50). The mounting shaft is of a generally hollow, tubular construction and serves as a conduit for perfusate from the supply tube to the aorta of the heart.

The chamber cover may also support a connector (120) carried by the extension (79) of the second side

wall (78) of the bubble trap. The connector (120) includes first and second cylindrical perfusate chambers (125,127) sealingly mounted to the first (80) and second (81) prime valve supply ports. The interiors of the two perfusate chambers communicate with one another through a tubular segment (129).

As shown in Figure 1, the invention includes a perfusate reservoir (133), desirably in the form of a flexible plastic bag, which supplies the system with perfusate solution. The perfusate reservoir is removably attached to one end of a perfusate reservoir line (134) so that the perfusate reservoir may be replaced when the supply of the perfusate fluid is depleted. The other end of the perfusate reservoir line may be connected to either the first (125) or second (127) chamber of the connector (120), and a supply line connector (136) is attached to the other chamber. Since the first and second chambers communicate with one another, perfusate may flow from the reservoir to the supply line connector (136) via the connector (120).

The connector (120) also includes an exit tube shown at (121) in Figure 1, disposed between the first chamber and the cover. Flange (131) of the connector is sealingly attached to the top (62) of the cover about an aperture (138) therein. Perfusate may flow downwardly from the first chamber through the exit tube and through the aperture (138) in the cover. A conduit (140) is attached at one end to the under side of the cover immediately below the aperture (138) to allow fluid to flow from the connector (120) to the conduit (140). At its other end, the conduit is sealingly attached to the under side of the valve slide plate (102) beneath an elongated slot (142) formed therein.

A resilient priming tube (144) is connected to the conduit (140) through the slot (142) and extends upwardly through elongated slots (146) and (90) formed in the top of the cover and the bottom plate (86) of the bubble trap, respectively. At its upper end, the priming tube is connected to a prime entry port (148) carried inside the bubble trap. The prime entry port communicates with the bubble trap interior through a one-way valve (149) which allows perfusate to flow from the priming tube into the trap, but prevents flow in the other direction. The prime entry port conveniently is formed in a cover plate (150) which is attached to the bottom plate (86) above the elongate slot (90) and seals the slot. The cover plate may also carry the air vent (152) of the bubble trap, which will now be described.

The air vent (152) comprises a tubing section which extends from the elongate slot (90) of the bubble trap's bottom plate (86) to a position spaced slightly below the top member (72) of the bubble trap. Preferably, a recess (154) is formed in the under side of the top member (72) so that any air within the bubble trap rises into the recess. A portion of this depression is located immediately above the upper end of the air vent so that this air may pass through the vent. An air vent tube (156) is connected to the air vent and extends downwardly next to the priming tube (144) through the elongate slots (90, 146 and 142) to allow air within the bubble trap to be vented through the cover and the valve slide into the heart chamber. If so desired, a short tube (158) may be connected to the air vent tube adjacent its lower end to hold the air vent tube in place. This short tube and the portion of the conduit (140) adjacent the valve slide plate may be carried on a

cover plate (159) which is attached to the valve slide plate and seals the elongated slot (142).

In an alternative embodiment (not shown), the three elongated slots are replaced with three pairs of holes, defining two discrete pathways from the interior of the bubble trap to the under side of the valve slide (100). The air vent tube is retained in one pathway while the priming tube is carried in the other pathway.

The top (62) of the cover also includes an exhaust port (160) which allows the interior of the heart chamber to communicate with the outside environment when the chamber cover is in place. This ensures that the interior of the heart chamber is maintained at atmospheric pressure even as air is expelled from the bubble trap into the heart chamber. An air filter (162 in Figure 1) is desirably placed over the exhaust port to maintain a sterile environment within the heart chamber.

Referring to Figure 1, an apparatus according to the invention also includes a pump (170, to be subsequently described) for controlling the rate of perfusate flow into the heart. A pump supply line (172) is connected at one end to the pump and delivers perfusate from the reservoir to the pump; a pump delivery line (175) is also connected at one end to the pump and delivers perfusate from the pump to the bubble trap. The platform (35) of the brace (30) includes means for retaining these lines adjacent the canister cover, such as appropriately shaped indentations (46,47) located adjacent the periphery of the platform. The pump supply line (172) includes a connector (173), adjacent the end disposed away from the pump, which mates with the supply line connector (136) located adjacent the connector (120). As

mentioned above, the first and second chambers of the connector (120) communicate, allowing the perfusate reservoir line (134) to communicate with the pump supply line (172). This allows perfusate to be drawn through the supply line via the connector (120). Connecting means (176) are also provided on the pump delivery line (175) for mating with the delivery line connector (76) carried by the first side wall (74) of the bubble trap. Perfusate flows from the pump into the bubble trap, and subsequently into the heart, through this connection.

Figures 3-5 show the valve slide (100) in its three primary control positions. As mentioned above, the valve slide includes a valve slide plate (102) with a supply orifice (104), which retains the perfusate supply tube (94), and an elongate slot (142), which retains the priming tube (144) and the air vent tube (156). A side wall (178) is carried between the periphery of the valve slide plate and the top member (62) of the cover.

A generally C-shaped bracket (180) is slidably retained between the valve slide plate and the top member (62) of the cover. The bracket includes two abutments (182) which extend inwardly toward one another from positions adjacent the ends of the arms (181) of the bracket. Each abutment engages the outer surface of one of a pair of obliquely angled bars (184) which is pivotally mounted to the valve side plate about a pin (185). A projection (186 in Figure 2) extends upwardly from the bracket through a valve control slot (188) formed in the canister cover. A manually graspable control knob (190) may be attached to the projection above the top member of the cover.

The valve slide is movable between three primary operating positions, shown in Figures 3-5. In its

first position, shown in Figure 3, the bracket (180) is disposed away from the second elongate slot (142). The abutments of the bracket urge the portions of the angled bars nearest the perfusate supply tube toward one another to pinch shut the flexible perfusate supply tube (94) to prevent perfusate from flowing out of the bubble trap into the heart. The air vent tube (156) and the priming tube (144) remain open in this position to allow perfusate to flow from the reservoir into the bubble trap through the connector (120) and the prime valve tube as the reservoir bag is manually squeezed to fill the bubble trap. As the bubble trap fills with perfusate, air is displaced from the trap through the air vent tube and into the interior of the heart chamber. Any excess perfusate will pass through the air vent and harmlessly collect at the bottom of the heart chamber.

Once the bubble trap is filled, the valve control may be moved to its second control position (shown in Figure 4) wherein the abutments of the bracket are disposed along the angled bars at a position adjacent the pivot pins (185) and all three valve tubes (144, 156 and 94) are open. Perfusate may flow downwardly to the heart from the bubble trap via the perfusate supply tube until the heart is filled with perfusate and the trap may be refilled through the priming tube by squeezing the reservoir bag. The bubble trap is maintained near atmospheric pressure by the air vent tube, which allows air to enter or be expelled from the trap.

Figure 5 shows the final operating position of the valve slide, wherein the bracket is disposed toward the elongate slot (142) of the valve slide plate. As the abutments of the bracket slide along the bars, they cause the bars to pivot further, urging

the bars into engagement with the priming tube and the air vent tube. These flexible tubes are pinched shut by the bars, preventing flow of liquid or air therethrough. This seals all exits from the bubble trap except the perfusate supply tube (94). As perfusate is delivered to the trap by the pump through the pump delivery line and the pump line port (75 in Figure 2), liquid is displaced from the trap into the heart at the same rate. One may thus control the rate at which liquid enters the heart by controlling the delivery rate of the pump.

The pump employed may consist of two elements of which one comprises an electrically (battery) driven driver which may cycle between two positions, and a compressible tubing coil which, as described, forms a portion of the conduit extending from the reservoir to the bubble trap. In its operative position, the tubing coil extends through a wall of the transport case into position so as to by cyclically compressed by the pump driver. One-way valves located on both sides of the tubing coil ensure perfusate flow only in one direction. The tubing coil may readily be disengaged from the driver for removal, with the heart chamber, reservoir and associated conduits as a sealed, sterile unit from the transport case. Pumps of the type thus described are commercially available, as from Frantz Medical Manufacturing.

Thus, the apparatus includes a closed, sterile system comprising the heart chamber (50), the chamber cover (60), and the pump tubing. The pump tubing is continuous and extends from the cover to the perfusate supply and the pump, through the tubing coil, and back to the cover; it includes the perfusate reservoir line (133), pump supply line (172), and the pump delivery line (175). This system is desirably formed of a

plastic material and may be discarded after a single use and replaced with a new, sterile system for use with another donor heart. The rest of the apparatus - including the pump (170), the transport case (10), and the brace (30) - may be reused with numerous new, sterile systems.

Figure 6 shows a schematic flow diagram for an apparatus of the invention. The numbers used in this diagram correspond to like numbered elements of Figures 1-5 which perform similar functions. The system includes a heart chamber (50), a chamber cover (60) and a pump (170). The perfusate reservoir (133) is connected to the system via a perfusate reservoir line (134). Fluid from the reservoir line may flow either into the bubble trap via the conduit (140) or to the pump (170) through the pump supply line (172).

Once the system is assembled with the heart attached to the mounting shaft (117) and the cover, the bubble trap (70) is filled. The priming valve (144) and the air vent valve (156) are in an open position while the supply valve (94) is closed to prevent flow therethrough. As the flexible reservoir bag is squeezed, perfusate is forced to flow from the reservoir through the conduit (140) and into the bubble trap. Before passing into the bubble trap, perfusate flows through the priming valve (144) and a one-way valve (149) which prevents flow in the other direction. As liquid enters the trap, air is displaced into the heart chamber via the air vent valve. Pressure within the heart chamber greater than ambient pressure is relieved through the air exhaust (162). Perfusate continues to flow into the trap until the trap is filled with liquid. If excess perfusate is inadvertently passed into the trap, it will flow out through the air vent and drain harmlessly to the bottom of the chamber.

Once the bubble trap has been filled, the heart is "primed" with perfusate. In this stage, all three of the valves (144, 156, and 94) are in their open position. Liquid within the bubble trap flows by gravity into the heart through the supply valve (94); ambient pressure is maintained through the air vent valve. As the bubble trap empties into the heart, more perfusate is supplied through the priming valve (144) by squeezing the reservoir bag.

When the heart is primed, i.e., filled with perfusate, and the bubble trap has been filled once again, the priming valve and the air vent valve are closed and the supply valve remains open. The pump is then engaged. Perfusate passes from the perfusate reservoir into the pump via the connector (120) and the pump supply line (172) and is delivered from the pump to the bubble trap via the pump delivery line (175). As perfusate enters the bubble trap via the pump line port (75), an equal amount of perfusate is displaced from the bubble trap into the heart. Perfusate exiting from the heart simply drains into the bottom of the chamber.

When the heart is primed, small bubbles of air may remain within the heart. These bubbles may become dislodged and pass up through the aorta into the bubble trap. Fluid immediately drains from the bubble trap into the heart to fill the void previously occupied by the air bubbles. If air bubbles thus rise into the bubble trap, they may be removed by moving the valve control to the position shown in Fig. 4 to open the prime valve and the air vent valve again, and supplying perfusate through the prime valve by squeezing the reservoir bag until the bubble trap is refilled with perfusate.

The system desirably is checked at least once every 30 minutes for the first two hours of operation to see that the bubble trap remains full. If the system is running properly, monitoring may then become less frequent since the likelihood of a pocket of air later becoming dislodged is small.

The apparatus of the invention may be used with any common perfusate. Desirably, however, the apparatus is used with a perfusate containing polyethylene glycol having an average molecular weight above about 15,000 daltons. An appropriate perfusate of this type is described in Wicomb, W.N. and Collins, G.M., 24 Hour Rabbit Heart Storage With UW Solution, Transplantation 48, pp. 6-9, July, 1989, which is incorporated herein by reference. The solution ingredients, including an impermeant composition, are chosen to be pharmacologically acceptable, and the solution desirably is buffered to a pH in the range of from about 7.1 to about 7.8, with a pH between about 7.1 and about 7.5 being preferred. The polyethylene glycol is free of material capable of being removed by filtration through a 10 micron filter or via membrane dialysis. The polyethylene glycol has an average molecular weight that is at least about 15,000 daltons, preferably is in the range of from about 15,000 to about 20,000 daltons, and is made through a process in which hydroxy-functional lower molecular weight polyethylene glycols are linked together using, as linking moieties, such diepoxides as the diglycidyl ether of Bisphenol A. Desirably, the concentration of the high molecular weight PEG in the preferred organ preservation solutions used in the apparatus of the invention is maintained in the range of about 4% to about 10% by weight. Approximately 5% PEG concentrations have yielded excellent results.

The high molecular weight polyethylene glycol employed in the preferred perfusate solution used with the apparatus of the invention provides unexpectedly good organ preservation capabilities. Although it is believed that in some applications the polyethylene glycol functions as a colloid to keep the perfusate in the vascular system, and that it may interact in some beneficial way with cell membranes, the precise technical explanation for the surprisingly beneficial properties of this material in organ preservation is not known.

The following example describes the use of the apparatus described above in connection with Figures 1 to 6 in a perfusion technique involving continuous hypothermic perfusion at very low rates:

The brace (30) is placed in the transport case (10) and the rest of the receiving well is filled with ice (20) or other cooling medium up to a level near that of the platform (35) of the brace. The donor heart is then excised via standard procedure, such as a median stenotomy, and weighed. The aorta of the donor heart is then attached to the mounting shaft (117 in Figure 2) and the connection may be checked by gently tugging on the heart. If the seal is not tight, the heart may be attached more securely. The mounting shaft is then fitted onto the chamber cover (60) as described above and the cover is placed on the heart chamber (50). The heart is thus suspended within the chamber from the mounting shaft. The cover retaining hooks (56) then engage the cover and the valve control (100) is placed in its first control position (shown in Figure 3).

The perfusate reservoir, which desirably has been chilled to between about 0° and about 10°C, is then connected to the bubble trap (70) and the bubble trap

is filled with perfusate. The valve control is then moved into its priming position (shown in Figure 4), allowing the heart to fill with perfusate. The operator should make certain that no air remains in the heart; the presence of air will be indicated by bubbles rising into the bubble trap after the initial drop in the perfusate level within the trap. If air does remain, the operator may carefully lift the cover off of the chamber and gently squeeze the heart to bleed out the air and replace the cover.

Once the heart has been primed and the bubble trap is refilled, as described above, the chamber may be deposited in the brace (30) of the transport case (10). The perfusate reservoir may simply be placed on top of the ice (20), which helps keep the perfusate chilled. Then the connecting means of the pump supply line (173) and of the pump delivery line (176) may be connected to the supply line connector (136) and the delivery line connector (76), respectively, carried by the chamber cover. Desirably, the pump supply line (172) and the pump delivery line (175) are then flushed with perfusate to remove air from the system prior to operation.

Once this has been accomplished, the pump is activated and set to the appropriate flow rate. As explained above, this flow rate desirably is from about 3.5 to about 6 ml/gram of heart weight/24 hour period. Since the heart being preserved has already been weighed, the net flow rate, which will generally be between about 175 ml and 3000 ml/24 hour period, may easily be determined and the pump is set accordingly. The valve control is then moved into the final, "run" position (shown in Figure 5) and the pump delivers a controlled volume of perfusate to the heart via the bubble trap. The cover (14) of the transport

case may be closed and the heart may be transported to its destination.

While a preferred embodiment of the present invention has been described, it should be understood that various changes, adaptations and modifications may be made therein without departing from the spirit of the invention and the scope of the appended claims.

CLAIMS:

1. A perfusion apparatus for preserving a heart during the quiescent period between harvesting from a donor and implantation in the chest of a recipient, comprising a heart-receiving chamber having an aortic connection from which a heart may be suspended by its aorta and through which the heart may receive perfusate solution, a reservoir of perfusate solution, conduit means communicating the reservoir with the aortic connection, a positive displacement pump for pumping perfusate solution from the reservoir through the conduit means to the aortic connection at a controlled rate.

2. The apparatus of claim 1 wherein the conduit means includes bubble trap means for receiving air bubbles emitted from a heart suspended in the chamber and for maintaining at least a one centimeter bubble-free column of perfusate above the aortic valve of the heart.

3. The apparatus of claim 2 including means for expelling air from said bubble trap means.

4. The apparatus of claim 1 wherein said cooling means includes heat exchanger means for drawing heat from the conduit means at a location between the pump and the aortic connection.

5. The apparatus of claim 1 including an insulating housing receiving the chamber, conduit means and reservoir.

6. The apparatus of claim 5 including framework means uniting the chamber, reservoir and conduit means and enabling these elements to be removed as a unit from the housing.

7. The apparatus of claim 6 wherein the positive displacement pump comprises an electrically powered pump driver carried exteriorly of the housing

and resilient tube means carried in series with the conduit between the reservoir and the aortic connection and cooperating with the electrically powered pump driver to receive perfusate from the resevoir and to pump the same to the aortic connection.

8. The apparatus of claim 7 wherein the resilient tube means extends exteriorly of the housing into removable operative association with the electrically operated pump driver.

9. The apparatus of claim 8 wherein the resiliant tube means comprises a compressible coil of tubing having check valve means at its ends to limit flow of perfusate through the coil means to a single direction, the coil means cooperating with and undergoing cyclic, volume-changing compression in response to operation of the electrically powered pump driver.

10. The apparatus of claim 2 wherein said bubble trap means comprises means defining an enclosure positioned above and in flow communication with the aortic connection, and valve means for expelling air from the enclosure and enabling the enclosure to fill with perfusate solution.

11. A perfusion apparatus for preserving a heart during the quiescent period between harvesting from a donor and implantation in the chest of a recipient, comprising an insulative housing, an exterior electrically powered pump driver, and a perfusion cartridge removably carried within the housing, the cartridge comprising means defining a heart-receiving chamber having an aortic connection from which a heart may be suspended by its aorta and through which the heart may receive perfusate solution, a reservoir of perfusate solution, conduit means communicating the reservoir with the aortic connection, and a positive

displacement pump element releasable from and cooperating with the electrically powered pump driver to pump perfusate solution from the reservoir through the conduit means to the aortic connection at a controlled rate of from about 175 to about 3000 ml per 24 hrs.

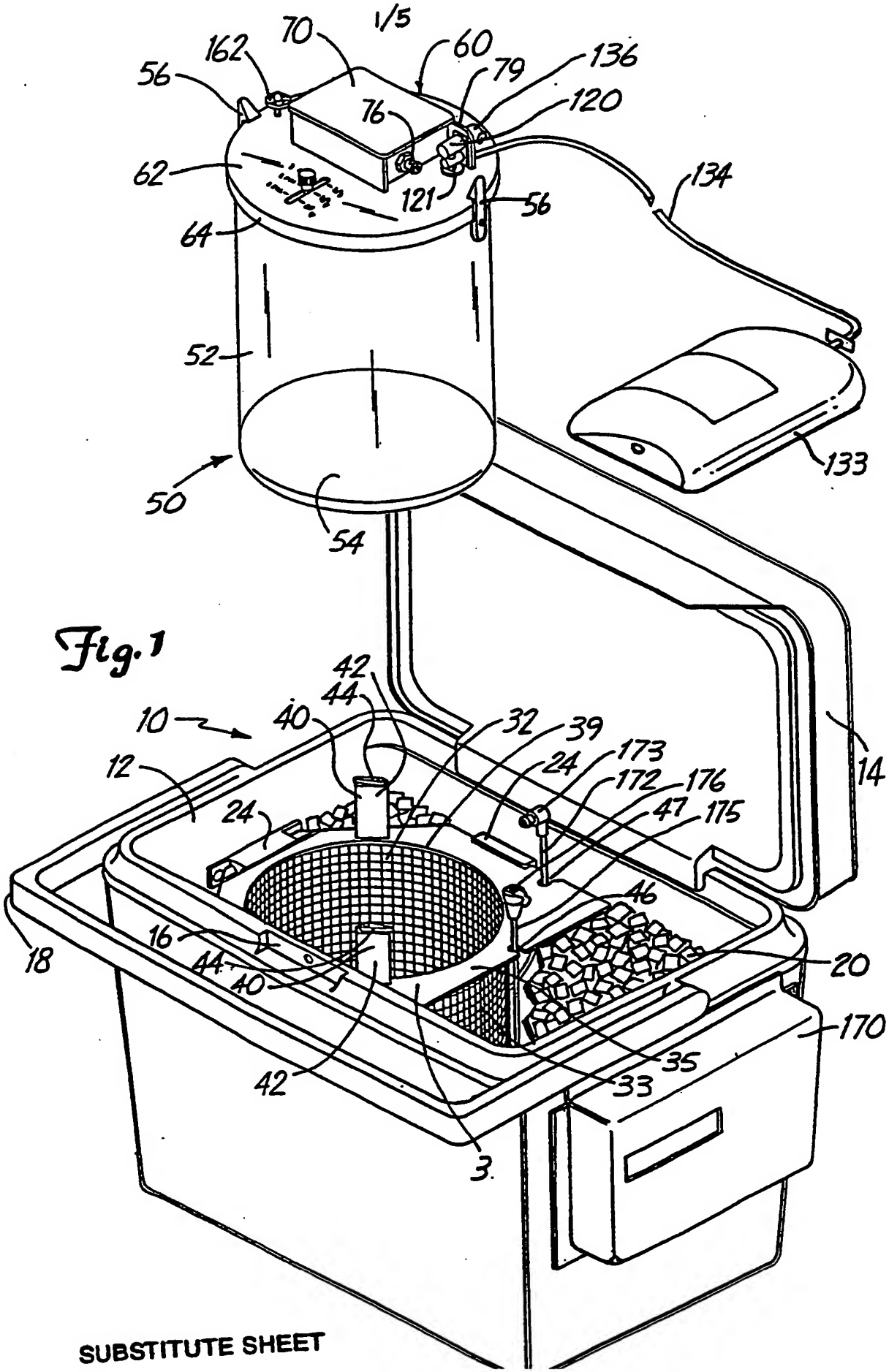
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Fig. 1

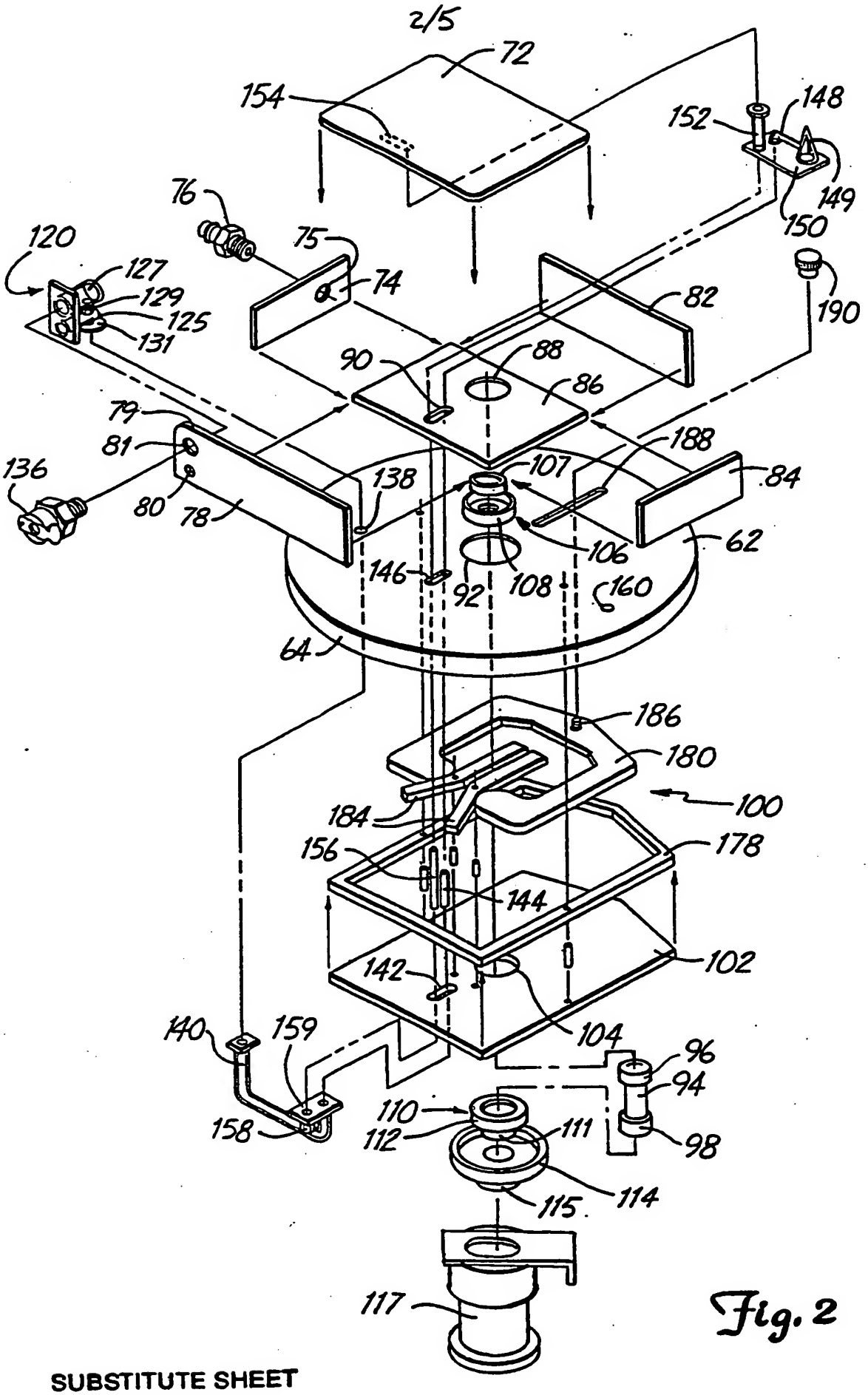
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Fig. 2

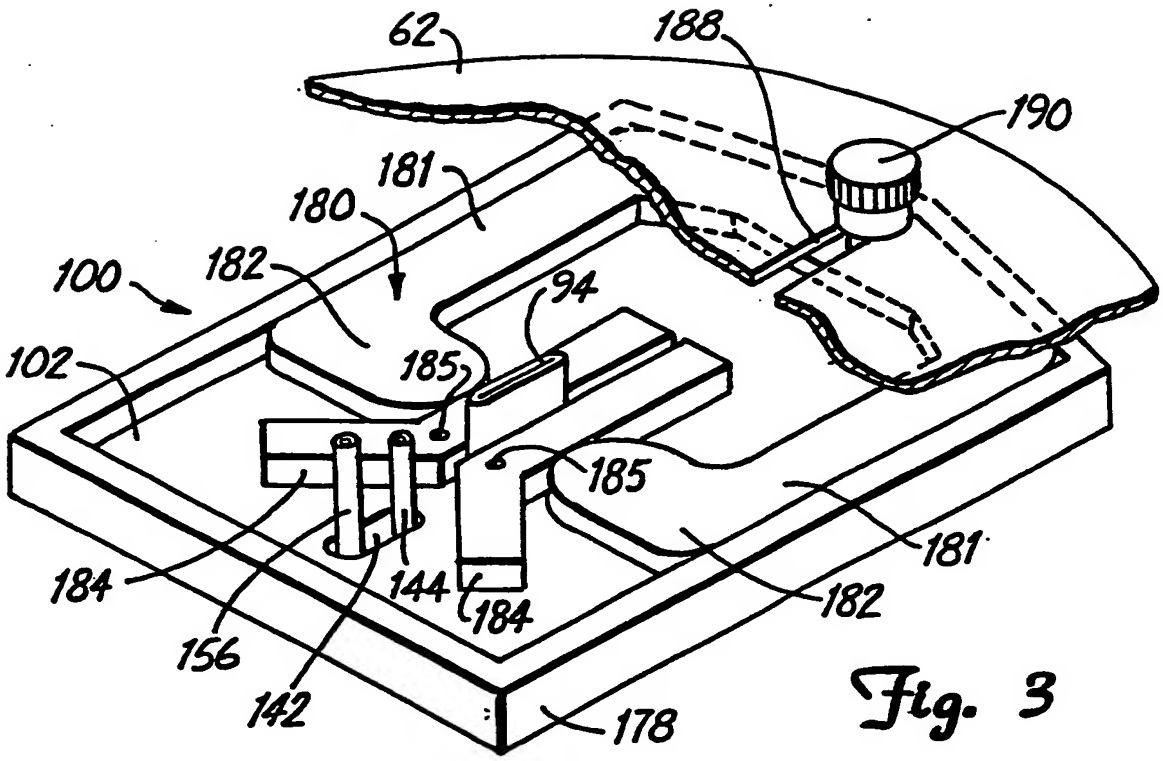
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Fig. 3

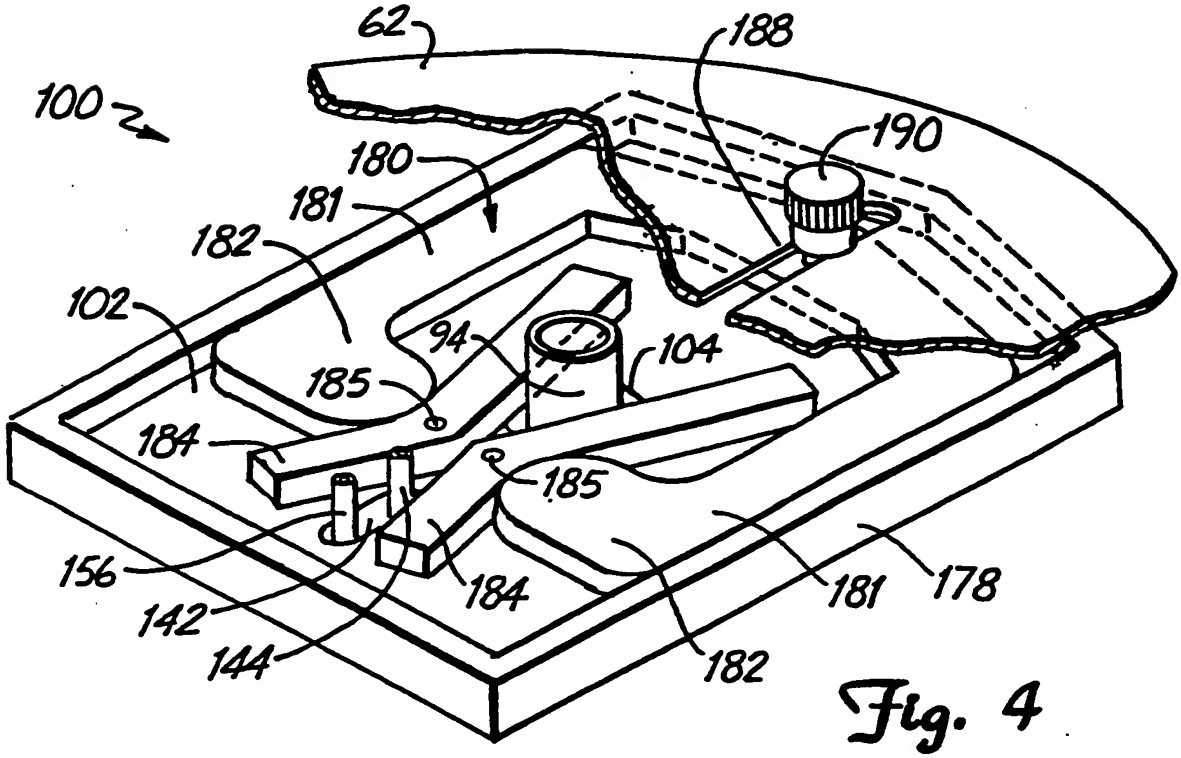
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Fig. 4

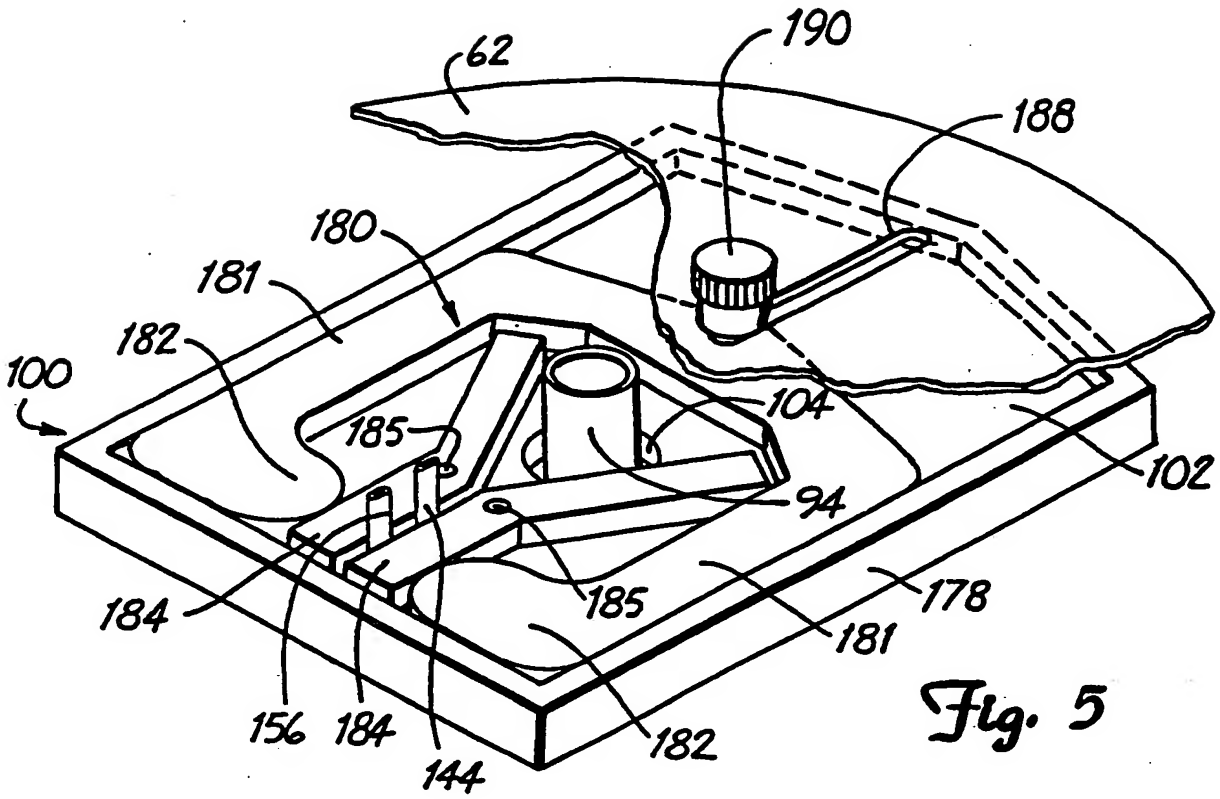
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Fig. 5

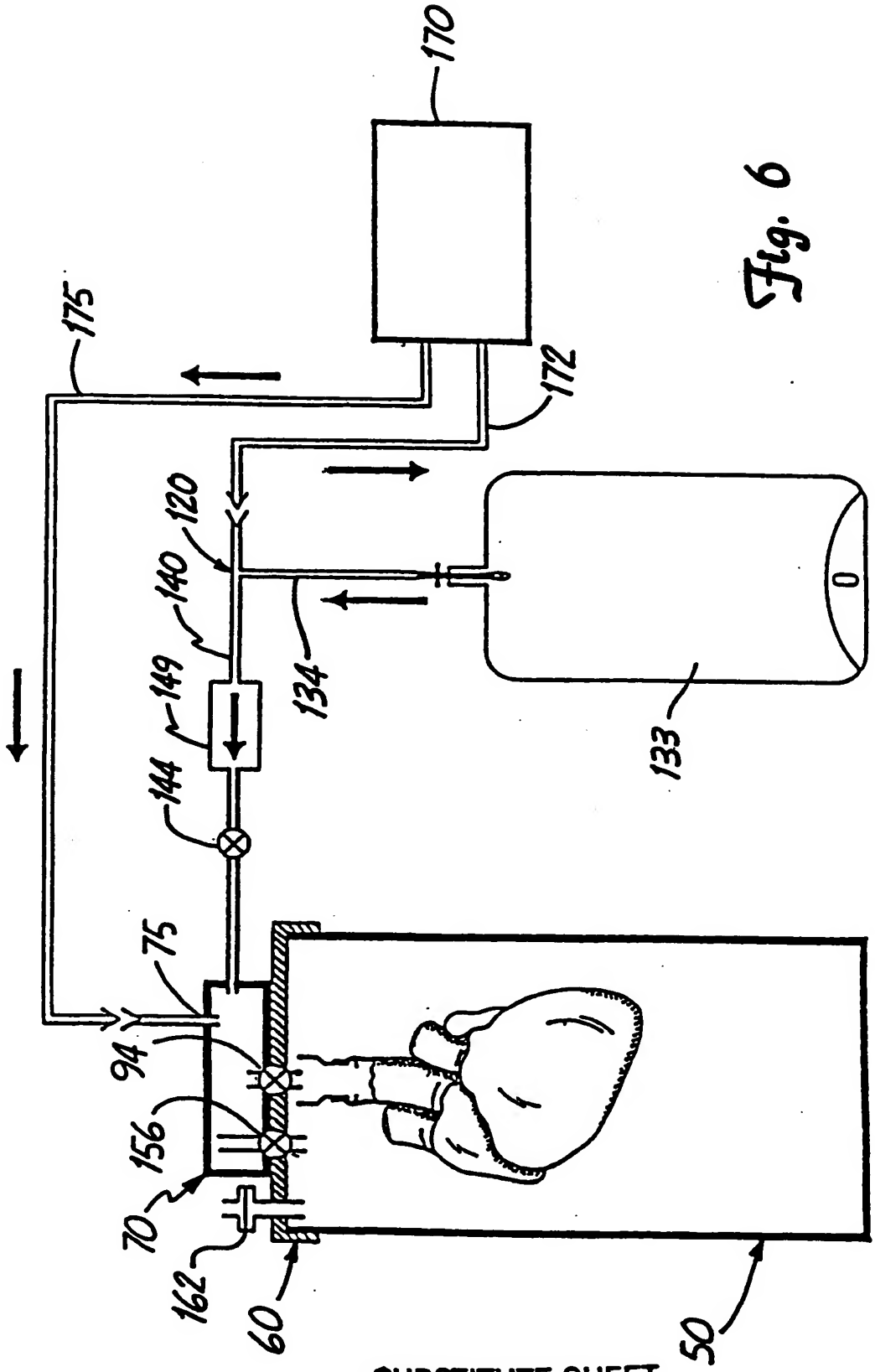

Fig. 6

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US91/02109

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC(5): A01N 1/02
U.S. Cl.: 435/1

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
U.S. Cl.	435/1, 283; 600/21; 604/4,122,123; 62/78

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
x y	Karow and Pegg, "Organ Preservation for Transplantation" published 1981 by Dekker, pages 477-495, see Figure 3.	1,2,4,5 3,6-11
Y	Journal of Heart Transplantation, Vol.5, No.2, issued March/April 1986, Wicomb et al., "Hemodynamic and Myocardial Histologic and Ultrastructural studies on Baboons from 3 to 27 Months Following Autotransplantation of Hearts Stored by Hypothermic Perfusion for 24 or 48 hours", pp.122-129, see Figure 1.	3,10
Y	US,A, 3,995,444 (CLARK ET AL.) 07 DECEMBER 1976, see entire document.	6-8,11

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
24 APRIL 1991	25 JUN 1991
International Searching Authority	Signature of Authorized Officer
ISA/US	WILLIAM H. BEISNER

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FURTHER INFORMATIO! ONTINUED FROM THE SECOND SHEET

Y	US,A, 3,753,865 (BELZER ET AL.) 21 AUGUST 1973, See entire document	9

V. ☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☐ Claim numbers .. , because they relate to subject matter [2] not required to be searched by this Authority, namely:

2. ☐ Claim numbers , because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out [3], specifically:

3. ☐ Claim numbers_____, because they are dependent claims not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

☐ The additional search fees were accompanied by applicant's protest.

☐ No protest accompanied the payment of additional search fees.